ONLINE FIRST

The Role of Early Resection vs Biopsy in the Management of Low-Grade Gliomas

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Gliomas are primary tumors of the central nervous system and are classified into grades I to IV according to histologic criteria. Grades I and II are low-grade gliomas and grades III and IV are considered malignant gliomas. Low-grade gliomas affect both children and adults. However, the predominant histologic type of glioma found in children is a grade I tumor, juvenile pilocytic astrocytoma, and is curable by complete surgical resection.

More problematic are the low-grade gliomas that occur in adults, referred to as grade II gliomas (LGGs). These tumors are characterized by an entirely different pattern of behavior. They are invasive and cannot be completely resected surgically; residual tumor cells are always present distal to the margin of resection no matter how extensive. Commonly, these tumors recur, eventually undergo malignant degeneration, and are ultimately fatal.

Considerable controversy exists in the neurosurgical and neuro-oncologic communities regarding the best approach for patients who present with imaging findings supporting a new diagnosis of LGG. Patients who undergo extensive resections of their tumors, in general, live longer. However, no randomized controlled studies have been conducted. Thus, there is a clear possibility of bias; that is, patients with tumors that are not selected by surgeons for resection, or those that undergo only minimal debulking, have poor prognostic features such as tumor location in or adjacent to important functional areas of the brain (eg, basal ganglia, motor, or language areas). Overly aggressive attempts at resection can leave these patients with permanent neurologic deficits.

Due to the lack of definitive evidence favoring resection, as well as the possibility of inducing a new neurologic deficit, surgical approaches to the management of these patients vary. Patients initially may undergo either observation, biopsy, or an extended resection. In the absence of definitive data, current treatment for LGG is not uniform and is often center or even surgeon dependent.

In this issue of JAMA, Jakola and colleagues take advantage of a distinctive referral scheme and an associated treatment approach to determine whether treatment of patients with LGGs using biopsy alone was associated with lower overall survival compared with patients receiving treatment by early resection.

The study design was the result of a unique situation in Norway in which 2 hospitals that are relatively close in geographic location have different treatment philosophies for patients with presumed LGG. One hospital used a biopsy followed by a watch-and-see approach, whereas another hospital used an early resection approach.

The study design was a retrospective intent-to-treat approach and was population based, because essentially all patients within the respective hospital's geographic referral area were treated at that institution. This study exploited the different philosophies in treatment approach as a means of patients being allocated into biopsy vs surgical therapy due to the preponderance of biopsies performed at one institution and early resections at the other. Presumably, the distribution of LGG histologic types, presentations, site of brain origin, and other features were randomly distributed between patients in the geographic catchment areas. Taking advantage of the centralized Norwegian health care system, no patients were lost to follow-up, strengthening the study results.

Study findings demonstrated that at the hospital favoring resection, patients had marked improvement in survival over time (an increase in survival initially apparent at 3 years) when compared with the patients treated at the hospital favoring biopsy alone (80% vs 70% survival at 3 years). This difference increased over time until, at 7 years, survival was 68% among patients at the hospital favoring a strategy of resection vs 44% at the institution favoring biopsy. A post hoc analysis suggested an increase in survival among patients diagnosed with grade II astrocytoma, ie, 9.7 years at the center favoring early resection vs 5.6 years at the center favoring biopsy. Biopsy was not determined to be significantly different from resection in terms of surgical complications, and malignant transformation, as defined by the appearance of new enhancement, was more common in the biopsy-only treatment group. Such a potential difference in survival provides important data to help inform the complex question of whether to attempt aggressive LGG resection.

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However, this study does have some limitations. First, as the authors note, the outcome assessment was determined retrospectively and thus is subject to reporting bias and crossover. In light of the difficulty of performing a randomized controlled study in this population, this is not a surprising limitation. Second, the CIs around the point estimates for survival in the 2 treatment groups overlap indicating that the findings could have occurred by chance. Continued follow-up of these patients will be needed to determine if the 95% CIs separate definitively with additional observation time. Third, there is a potentially important difference between the groups in the fraction of patients with oligodendrogliomas (19% vs 9%) in the resection group and in the biopsy group, respectively. Oligodendroglioma has a 5-year survival of nearly 80%, compared with 5-year survival of less than 50% for astrocytoma. Post hoc analysis suggested that even the patients in the low-grade astrocytoma category fared better at the institution favoring resection, although this finding should be considered hypothesis generating. Fourth, there were some other differences in treatment strategies: early postoperative radiation therapy was administered more commonly at the center favoring resection (43%) vs the center preferring biopsy alone (29%). Although no difference in survival has been demonstrated with radiation in at least 2 different studies of LGG, the findings of this study may reflect outcomes associated with resection plus radiation in this cohort comparison. Fifth, the question of risk related to resection procedures remains unanswered. Although this study suggests there was no difference in complications or neurologic deterioration between the 2 studied groups, assessment methods were not delineated and the data were insufficient to reach a definitive conclusion.

Over the past 25 years, increasing numbers of studies support the concept of maximizing the extent of resection in patients with glioma while maintaining neurologic function; however, no class I evidence exists for this approach. A recent review of LGG identified 16 studies that have statistically examined the association of extent of resection with survival; the vast majority were reported to support increases in either 5-year survival, 5-year progression-free survival, or both. However, at least 1 large study showed no difference. Other studies have suggested that more aggressive resection may decrease the rate of malignant transformation.

Although class I evidence for surgical resection of LGG remains lacking, National Comprehensive Cancer Center practice guidelines in oncology support maximal safe resection as a feasible first line of treatment for LGG. The majority of these studies, but not all studies published in the past 2 decades, support this approach as well. The study by Jakola et al adds further evidence for this approach. A follow-up study of their cohorts, allowing for more definitive measurement of survival and more rigorous assessment of complications, neurologic deterioration, and malignant degeneration, would be valuable.

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REFERENCES